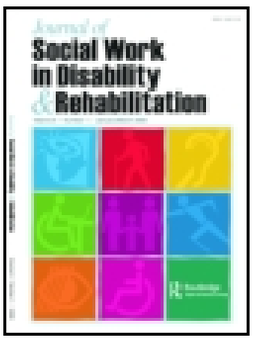

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Environmental Exposures to Metals in Native Communities and Implications for Child Development: Basis for the Navajo Birth Cohort Study

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Two disparate statistics often cited for the Western United States raise concern about risks for developmental disabilities in Native American children. First, 13 of the states with the highest percentage of Native American population are located in the Western United States (U.S. Census Bureau, 2012). Second, more than 161,000 abandoned hard-rock mines are located in 12 Western states (General Accounting Office, 2014). Moreover, numerous studies have linked low-level metals exposure with birth defects and developmental delays. Concern has emerged among tribal populations that metals exposure from abandoned mines might threaten development of future generations.

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More than 161,000 abandoned hard-rock mines are located in 12 Western states (General Accounting Office [GAO], 2014). Thirteen Western states have the highest percentage of Native American population in the country (U.S. Census Bureau, 2012), creating concerns about the potential for Native American communities in the West to experience disproportionate exposures to mixtures of heavy metals associated with developmental delays and disabilities. Abandoned uranium mines account for more than 4,000 of the 161,000 abandoned hard-rock mines (U.S. Environmental Protection Agency [U.S. EPA], 2008a). In Navajo Nation specifically, more than 500 abandoned mines remain as the legacy of Cold War mining. These mine wastes represent mixtures of metals including not only uranium, but also arsenic, copper, and other heavy metals, as well as remaining radionuclides. No systematic investigation has been undertaken to understand how exposures in the numerous rural tribal communities in proximity to these wastes might affect health, especially in children. The mine sites are most often unmarked, unfenced, and the historical memory of their location is being lost in the communities. Our research team, working with many Navajo communities, has observed children in direct contact with these mixed metal wastes (see Figure 1). Many successive generations in the communities have grown up in close proximity to these wastes, both during the active mining era and now, when the unremediated legacy wastes remain in their communities (see Figure 2). In 2007, in response to numerous requests from Navajo Nation and affected communities (McSwain, 2007), Congress implemented

FIGURE 1 Navajo children walking at the foot of unremediated uranium mine waste pile circa 2007.

FIGURE 2 Navajo child watches as 18" of contaminated soil is removed from his community. Note gray uranium mine waste pile in upper right. Additional mine waste is located to his left.

the first steps to address this problem through a Five-Year Plan to address uranium contamination on the Navajo Nation (U.S. EPA, 2008b). In 2010 the first health study was added to that plan to understand the relationship between exposures to uranium mining wastes, birth outcomes, and developmental delays in this population: the Navajo Birth Cohort Study (NBCS). Authors of this paper are members of the NBCS study team, including Dr. Lewis, NBCS Principal Investigator. No systematic assessment of the prevalence of adverse birth outcomes and developmental disabilities or delays has been done in this population, despite early suggestions of a potential link between these exposures and congenital malformations (Shields, Wiese, Skipper, Charley, & Benally, 1992).

In this article, we discuss (a) the basis of community concerns for child development in relation to exposures from both the community and the literature perspectives; (b) how the problem is being investigated; and finally (c) some preliminary findings that we will build on in the coming years to answer these questions. Barriers to treatment and diagnosis that contribute to our lack of information and limit care, and the efforts of our partners to address those barriers, are also discussed.

CASE STUDY VIGNETTE: HELEN NEZ, TACHEE-BLUE GAP, NAVAJO

The story of coauthor Helen Nez, a member of the Tachee-Blue Gap community on Navajo Nation in northeastern Arizona, illustrates the concern

and stress many Native Americans experience when faced with the uncertainties of what causes disabilities in their children, and their questions over what they can do to ensure that their babies grow up and have long, healthy lives: lives that allow them to Grow in Beauty. Her story, as told to NBCS media specialist and coauthor Malcolm Benally, also illustrates the need for these parents to have access to adequate and informed clinical and social networks to support their children's health struggles. Helen's story, which follows, highlights several questions that remain unanswered today regarding prevention, diagnosis, and care of Native children with disabilities.

Helen's Story

Helen has lived her whole life in the Blue Gap Chapter of the Navajo Nation near Tachee, Arizona (see Figure 3). Her first child was born when she was a 25-year-old woman. She had 11 children. One of her children was stillborn. She lost six additional children to Navajo neuropathy, a disability that was not recognized at the time. Three of her children—Jerome Nez (1967–1970), Claudia Nez (1970–1972), and Euphemia Nez (1975–1978)—all died before their third birthdays. Their stomachs had become bloated and their eyes became a cloudy gray color as they became sick. Her daughter, Dorenta Nez, spent a month at the hospital in Albuquerque, New Mexico (131 miles away) when she became ill. Her stomach had also become bloated and she died coughing up blood when she was 3 years old in 1978. Two of Helen's children lived into early adulthood. Theresa Nez lived to be 25 years old. She began dialysis treatments at the age of 19 and died of kidney failure.

FIGURE 3 Helen Nez in her home in Tachee-Blue Gap, Arizona.

Cedar Nelson Nez lived to the age of 35 years. Helen's four surviving children are now adults and talk not only about their own milder disabilities and recurring health problems, but about the impact of seeing so many of their family members suffer and die in such a short time, one likening the impact to posttraumatic stress disorder.

Through all of her ordeals with each child, their help and support came from the local Catholic Church, Navajo and Hopi medicine men, and a social worker named Alta Earl. An advocate, Cherie Daut-Neztsosie from Tuba City, Arizona, had begun helping Helen document her children's conditions, but Cherie passed away 20 years ago before completing the task. At one point, when Helen was determined to get medical help for her children, she was escorted out of the Chinle, Arizona, hospital by security. Western medicine could only say that the children's conditions were genetic and nothing could be done.

A physician who cared for Dorenta in Albuquerque, Dr. Snyder, was the first to suggest to Helen that the area where she lived might be contaminated with hazardous materials from prior uranium mining, and that exposure to the waste might contribute to the neuropathy. It was Dr. Snyder and his colleagues who finally identified the disabilities in Helen's family as Navajo neuropathy in 1976 (Appenzeller, Kornfeld, & Snyder, 1976).

COMMUNITY CONCERNS ABOUT POTENTIAL ENVIRONMENTAL LINKS

The frustration on the part of both those affected and of providers who can offer no solutions is clear in Helen's story. The neuropathy that Helen's children struggled with results in multisystem degeneration involving the liver, central and peripheral nervous systems, and the immune system, among others. The disability is accompanied by a failure to thrive and often results in premature mortality due to liver failure. In 40% of children affected, this occurs in their teens. The average age of death is 10, and onset generally is in the first year of life. The prevalence of this disability in the Navajo population is now recognized to be as high as 1 in 1,600 live births in certain geographic regions of the Navajo Nation (Karadimas et al., 2006). As illustrated by Helen's story, this disability can affect multiple members of individual families, creating even more significant impact than suggested by the prevalence.

Helen's community is one of many affected by the mining of uranium to meet Cold War weapons development demands in the United States. Helen's home during the active mining period of the mid-1950s to the late 1960s was located about 1 to 2 miles south of a series of what are now abandoned mines that were operational during her childbearing years, opening in 1957. For the Nez family and others similarly affected, their questions as to the cause of

their children's disabilities have continued to focus on the uranium exposures (Pasternak, 2011; Rosen & Mushak, 2000), in spite of indications that a genetic anomaly is involved (Karadimas et al., 2006). Two of the Nez family's main water sources during Helen's childbearing years were a windmill at a now-abandoned school site and a natural spring located about a mile from their family home. The windmill, which was closed in 1999, had evidence of contamination by manganese in a sample collected by federal scientists in 1998, long after Helen drank from the well. No historic water quality data for this windmill exist in available records. The spring, which was identified by Helen's adult son Christopher and is now covered with mine wastes, had a uranium concentrations more than five times the U.S. EPA maximum contaminant level when tested in 2014 by the University of New Mexico (UNM) METALS team (see UNM, 2014). Our research team has found no historic water quality data for this spring in available records to compare with the recent results. Even if samples had been collected from both sources during Helen's childbearing years in the 1960s and 1970s, uranium and other metals were not routinely tested for in water sources during that era.

On the Navajo Nation, greater than 30% of the population lacks access to clean, regulated drinking water, and therefore historically they have used a variety of unregulated and therefore untested sources for their drinking water. In Helen's case, she, like many others, did not understand the potential hazards of uranium mines until concerns were expressed by her chapter in the late 1980s. Helen's story has been repeated by several other women and has generated hypotheses linking prenatal uranium exposure to development of Navajo neuropathy in the book *Yellow Dirt* by Pasternak (2011), as well as in evidence in a toxic tort case (Rosen & Mushak, 2000).

A mitochondrial genetic mutation (MPV17) has been identified in those affected with Navajo neuropathy (Karadimas et al., 2006), but the prevalence of this mutation in the overall Navajo population has not yet been investigated. Nor have gene–environment interactions been investigated whereby exposures might influence expression of a genetic susceptibility for a disease or condition. Rather, the link of Navajo neuropathy to a genetic mutation has caused researchers to attribute the condition to a "founder effect" whereby it is hypothesized that genetic diversity in the population was reduced following the Long Walk of the Navajo people to Fort Sumner, New Mexico, in 1864 (Karadimas et al., 2006).

This founder effect has over the years been ascribed as causation for the increased prevalence of severe combined immunodeficiency (SCID), Navajo neuropathy, Navajo poikiloderma, and Athapaskan brain stem dysgenesis, all occurring at higher than expected prevalence in the Navajo population (Erickson, 1999). Although such historical events, which result in major population reduction, have commonly been associated with increased frequencies of recessive alleles, other researchers have pointed out that

pedigree analyses on Navajo have not supported that hypothesis in this case (Jones, Ritenbaugh, Spence, & Hayward, 1991). These researchers note that Navajo marriage rules, which prohibit marriage into either the mother's or the father's clan or to members of related clans, have had the opposite effect in this culture. Their pedigree analyses suggest that rather than increased homozygosity that would result from the inbreeding predicted from the founder effect, there might be excess heterozygosity associated with the maximized outbreeding maintained in the culture. Also, common ancestors could only be identified in 3 of 13 families affected by Navajo neuropathy in a 1990 study (Singleton et al., 1990). The fact remains that there has never been an investigation of potential gene–environment interactions, or a systematic evaluation of the role of environmental exposures on Navajo or their link to potential genetic susceptibilities for Navajo neuropathy or other disabilities at higher than expected prevalence in this population.

UNANSWERED QUESTIONS

The questions that remain unanswered for Helen Nez, her community, and thousands of other Native Americans affected by the legacy of uranium and other metal mining today include the following:

1. Has anything been done to improve diagnosis and treatment of childhood disabilities since Helen's experience?
2. Are community concerns about exposures to environmental metal contaminants and the health of their children and future generations well founded?
3. Could environmental contaminants interact with genetic factors to trigger disabilities?
4. How can we further our understanding of relationships between exposure and disease to answer the questions in our Native communities?

As noted in articles throughout this issue, our knowledge of disabilities in tribal communities remains limited. The lack of understanding of severity, type, and causes of disabilities, combined with the limits in infrastructure and resources for clinical and social service support within many Native communities can hamper the provision of optimal care and support to affected families. Further complications arise from cultural differences in the perception of disability, and the lack of discussion of the problems associated with disability in Native American communities, within the scientific literature and in the academic realm in which medical and social services professionals are trained. Differences across states in how disabilities are identified and tracked further complicates our understanding, as does the small number of tribal members represented in state databases and inability to access

tribal-specific data within compiled data sets in many states. Data compiled from birth records will not be consistent with those compiled over the first few years of life to pick up anomalies not clearly presented at birth. Data sharing agreements in some states have not been established with tribes, limiting ability to access tribal-specific data within the state-compiled data sets. Lack of tribal resources often limits the ability for tribes to track cases internally, and failure to report data from tribal populations further limits the accuracy of state data.

In the remainder of this article, we summarize what is known to answer Helen's questions. Helen's community is representative not only of many isolated Native American communities in the West, but also of other rural communities impacted by tens of thousands of abandoned hard-rock mines, a subset of which are abandoned uranium mines from the Cold War era. Therefore, answering Helen's questions will have relevance for all of these communities living in proximity to these abandoned sites.

Has Anything Been Done to Improve Diagnosis and Treatment of Childhood Disabilities since Helen's Experience?

As highlighted in a 2009 review, 7.9 million people are born each year with a birth defect; 3.3 million a year die before the age of 5 from the defect; and 3.2 million of those surviving face mental or physical disability for life (Weinhold, 2009). In the words of Ted Schettler, Science Director for the nonprofit Science and Environmental Health Network, classification and data challenges in surveillance of birth defects almost makes cancer tracking look easy (Weinhold, 2009). Systematic assessment of developmental delays and disabilities resulting from congenital malformations in tribal communities is difficult. Several factors likely contribute to the underestimation of actual prevalence in Native populations. These include the relatively small numbers of affected individuals, which limits the ability to extract reliable estimates from larger state or national data sets; differences in perceptions of disabilities in tribal cultures, which might lead to a lack of recognition within affected families; and the lack of infrastructure and resources for diagnosis and service, or the willingness to access those available.

Even in states such as New Mexico where Native Americans represent approximately 10% of the population (U.S. Census Bureau, 2012), or Arizona with 4.6% of the population, tracking methodology for birth defects differs substantially, as do agreements on data sharing, making it difficult to compare or integrate results. For example, differences in birth defect tracking include whether or not congenital defects are tracked at birth only or over a number of years often required for diagnosis; whether only live births are included, or also stillbirths and elective terminations; whether the frequency of occurrence and the population size are sufficient to establish prevalence within states; and whether adjusted or raw data are available.

These differences hamper the ability to make comparisons and to pool data across states to establish representative Native American prevalence estimates for most congenital anomalies.

A recent study has attempted to overcome these barriers, working with birth defect surveillance data from 12 states with consistent methodology over an 8-year period ending in 2008. This work documented a substantially higher prevalence in Native Americans and Alaska Natives for 8 of 27 tracked birth defects. The adjusted prevalence of seven of the eight birth defects (anotia or microtia, trisomy 18, cleft lip with or without cleft palate, lower limb deficiency, encephalocele, upper limb deficiency, and any limb deficiency) was 50% higher or more among Native children than among non-Hispanic White children (Canfield et al., 2014). Adjusted prevalence of anotia or microtia was sixfold higher than in the lowest racial or ethnic group (non-Hispanic Blacks), with the next four of the listed defects nearly double in adjusted prevalence compared to non-Hispanic Whites. Only two conditions were found at lower prevalence in American Indians and Alaska Natives: hypospadias in males, and pyloric stenosis. The Canfield et al. (2014) study was the first multistate estimate for American Indians and Alaska Natives. However, of the 12 states included in the study, only 2 have greater than 1% Native population, and none of the six states with the highest percentage of Native populations in the 2010 Census were included. For example, when looking at defects such as Down syndrome that had relatively similar prevalence across groups, the prevalence was based on 110 cases for Native Americans and 17,006 cases for non-Hispanic Whites. Therefore, although this is the most comprehensive assessment of rates of birth defects to include Native Americans to date and represents 37% of all U.S. live births from 1999 to 2007, the relatively small numbers of Native Americans within the data set makes it difficult to know how representative it is of the actual rates for Native Americans. Moreover, the study did not look at environmental risk factors.

Severe disabilities with genetic components such as those discussed previously are somewhat more frequently documented in the literature. On the Navajo Nation, for example, the prevalence of SCID is approximately 52 per 100,000 compared with 1 per 100,000 in the general U.S. population (Lipstein et al., 2010). Again, this severe disability is known to have a substantial genetic linkage along with other immunologic disorders found at higher prevalence among members of the Navajo Nation, but is not geographically homogeneous in distribution throughout the tribe (Jones et al., 1991), and questions as to gene–environment interactions, epigenetic factors, and the overall prevalence of specific genetic markers in the population remain. For Navajo, current policy on human research has placed a moratorium on genetic research, maintained through review by the Navajo Nation Human Research Review Board, making it likely these uncertainties will remain for some time.

New Mexico is home to almost 220,000 Native American citizens. Nineteen Pueblo tribes, two Apache tribes (Jicarilla and Mescalero), and the Navajo Nation comprise 10.5% of the state's population (New Mexico Indian Affairs Department, http://www.iad.state.nm.us/history.html). Many families live in rural communities, with limited access to resources, including health care and educational programs. Families who have children with medical or developmental needs are affected by the rural nature of communities, as they have limited availability of providers with expertise in diagnosis and intervention. As a result, many families with children requiring early intervention are referred to larger, metropolitan areas where specialized service providers are available, but where logistical or cultural barriers either prevent or significantly interfere with families receiving services. The University Centers of Excellence on Developmental Disabilities (UCEDD) and Native American Research and Training Center at the University of Arizona have found a range of barriers to receiving care in metropolitan areas ranging from transportation barriers to a lack of support and resources outside of their home communities. Further, Native individuals with developmental disabilities and their families want service systems to respect their culture and customs and provide information, training, and services that are relevant and appropriate.

The Indian Children's Program (ICP) was a collaborative project formed by UCEDD programs at Utah State University, Northern Arizona University, and the University of New Mexico. Started in 1991, the ICP provided family-centered and community-based services to Native American children with disabilities living in the Four Corners area of Utah, New Mexico, Arizona, and Colorado. ICP addressed critical service needs for children with disabilities in Native American communities. In addition to diagnostic services, ICP provided case coordination, therapeutic services, training, and technical assistance. In November 2014, after 23 years of service, the ICP was disbanded, leaving a large gap in service coordination and delivery to this already underserved community.

Navajo Nation is meeting this gap in services through its own early intervention referral program: Growing in Beauty (GIB). GIB is a component of the Office of Special Education and Rehabilitation Services of the Diné Department of Education and supports and promotes opportunities for young Navajo children and their families to receive appropriate developmental services and early intervention. GIB respects and recognizes traditional beliefs of child development. Whereas Western developmental milestones help predict the next phase of a child's growth, traditional Navajo recognition of the baby's and child's life steps helps guide his or her health, safety, and personality into adulthood.

GIB implements a team-based or transdisciplinary mode, assuring that families have access to a full team of individuals representing diverse disciplines including a service coordinator, physical therapist, occupational

therapist, speech therapist, and developmental specialists with expertise in autism, regulatory disorders, sensory impairments, and other developmental disabilities. The GIB staff serve as a "guide" through the initial stress and confusion of having a child diagnosed with a disability by coordinating services and helping anticipate family priorities and concerns, recognizing strengths and advocating for the Navajo family. This can include access to traditional healing ceremonies for families.

In 2014, GIB served 1,102 infants and toddlers (birth to 3 years), 735 from New Mexico. Eligibility criteria for early intervention in New Mexico are broader and include environmental risks, accounting for the increased percentage of New Mexico children. GIB works closely with the University of New Mexico Center for Development and Disability (CDD) in provision of services. In 2012, CDD experienced the barriers to services previously discussed when Navajo families missed 12% of appointments in the first 6 months of the year. CDD also found that as a result of differences in Navajo versus Western beliefs about child development, families often did not recognize the need for or importance of a developmental evaluation. To overcome the physical and cultural barriers to services, CDD collaborated with ICP to structure more effective service delivery, and now travels to Navajo Nation to complete evaluations in the community. CDD works closely with Native American professionals in organizations such as ICP and GIB as cultural liaisons to provide guidance and feedback on culturally sensitive practices and support for communication in their Native language. As a result, virtually all families currently are attending scheduled appointments and families are receiving specialized evaluations and intervention services when appropriate.

Even when families are able to access these services, clinicians have limited information from the scientific research literature to guide culturally sensitive practices surrounding developmental disabilities in Native Americans. To our knowledge, normative data for developmental delays in Native children are either very limited or unavailable for either clinician-administered developmental assessments or parent questionnaires. Clinicians often use assessments (Mullen, 1995; Bayley, 2006; Bricker, Squires, Kaminski, & Mounts, 2006; Squires, Bricker, & Potter, 1996), such as the Mullen Scales of Early Learning, the Bayley Scales of Infant and Toddler Development–Third Edition, or the Ages and Stages Questionnaire as measures of a child's abilities with the caveat that the scores are an estimate of the child's functioning because normative data are not available for Native American populations. The risk in this approach is that a child could be nondifferentially misclassified as either having or not having developmental concerns due to the lack of culturally appropriate normative data. Given the lack of available alternatives, these assessment tools continue to be used.

Recognizing the problem presented by the lack of standards appropriately normed for the culture, the NBCS is working with the developers of the Ages and Stages Questionnaire, with permission from Navajo Nation

Human Research Review Board, to develop Navajo-specific norms based on the anticipated 1,500 children in the birth cohort study. As this instrument forms the initial screening tool for GIB, culturally appropriate norms will provide more accurate identification of at-risk children. The administration of the screening instrument to all participants in the NBCS will also allow a broader characterization of the percentage of children at risk, and the types of delays most prevalent to further inform the activities of both GIB and CDD, who are partners in the study.

Are Community Concerns About Exposures to Environmental Metal Contaminants and the Health of Their Children and Future Generations Well Founded?

Although the prenatal period is recognized as a very vulnerable time, and birth defects are known to contribute significantly to lifelong mental and physical disabilities, limited research has investigated the relationships between in utero exposures to contaminants and birth outcomes. Even less research has examined racial and ethnic differences in exposure–birth outcome relationships and the effects of exposures to mixtures of contaminants. Existing work has shown in utero exposures to arsenic, lead, and mercury, in addition to other environmental contaminants, can be directly linked to specific birth defects (Weinhold, 2009). Much current scientific evidence demonstrates that environmental exposure beginning in utero can affect infant, childhood, and adult health conditions (Burton, Barker, Moffett, & Thornburg, 2011; La Merrill & Birnbaum, 2011; La Merrill et al., 2013). Children, from birth through age 12, are particularly susceptible to the toxic effects of environmental exposure (Au, 2002). As mentioned in the beginning of this article, Native American communities have disproportionately high exposure potential to waste metals from abandoned hard-rock mines in the Western United States. Mining regions specifically have vast areas of disturbed soils contaminated with a variety of environmental metals including arsenic, lead, nickel, uranium, vanadium, copper, and iron, as well as many others depending on the location and type of minerals being mined (Ahern et al., 2011; Wu, Zhang, Pei, Chen, & Zheng, 2014). More than 161,000 abandoned hard-rock mines are located in 12 Western states (GAO, 2014)—the same states that have the highest percentage of Native American population in the country (U.S. Census Bureau, 2012)—providing ample opportunity for maternal and child exposures to environmental metal mixtures. However, little scientific evidence is available to help us understand the degree and types of risks associated with metals from mining operations and pregnancy outcomes among Native populations. As mentioned, uranium mine waste presents a risk at more than 4,000 of the abandoned mine sites, and is the major waste source in the Navajo Nation affecting the participants in the NBCS, so we start with that body of evidence.

To date, most of what is known about uranium-induced developmental toxicity has come from experimental work performed in animal models. Effects including decreased fertility, embryo and fetal toxicity including teratogenicity, and reduced growth rate of offspring have been observed following uranium exposure at different gestation periods (Domingo, 2001). These reproductive effects are based primarily on the chemical nature and properties of uranium rather than its radioactivity. Despite the large numbers of Native women who live in regions with heavy uranium mining history, only one study has evaluated the risk of adverse outcomes of pregnancy in relation to uranium exposure from mining and milling operations. This study, which included more than 13,300 Navajo children born at the Public Health Service/Indian Health Service Hospital in Shiprock, New Mexico, was the first to describe a link between living near uranium tailings or mine waste dumps and adverse birth outcomes in a Native population (Shields et al., 1992), although a possible confound of exposures at an electronics plant limited the interpretation of those data. More than two decades later, initial biomonitoring results from the NBCS indicate that a higher percentage of mothers in our study show evidence of continuing exposure to uranium as measured in urinary uranium, with 81.2% of mothers at enrollment during pregnancy exceeding the 50th percentile, and 16.1% exceeding the 95th percentile observed for the U.S. population as a whole as reported in the National Health and Nutrition Examination Survey (NHANES; Centers for Disease Control and Prevention [CDC], 2013).

Beyond the scant population-based evidence already described, there is little else to inform the risk association between uranium and other metals from mining operations and pregnancy outcomes in Native populations. However, information from other populations does support concerns about the risks for birth defects and child development. For example, living in close proximity to surface coal mines has been associated with birth defects involving the circulatory and respiratory system, the central nervous system, and musculoskeletal, gastrointestinal, and urogenital defects (Ahern et al., 2011). In addition to organic toxicants, coal also contains mixtures of metals. Elevated arsenic and lead in soils near the homes of mothers during pregnancy in areas of coal mining and down gradient of coal mining have been associated with neural tube defects (Wu et al., 2014). Evidence linking birth defects to metals exposure has also emerged from Iraq, where mercury, lead, and depleted uranium (metal components of bullets and other ammunition) were six times higher in hair samples from children with birth defects (heart defects, neural tube defects, and cleft lip or palate) and five times higher in their parents compared to normal children and parents. Lead levels in teeth were also higher in parents and their children for children with anencephaly, hydrocephalus, limb deformities, omphalocele, or short extremities compared to unaffected children and parents (Al-Sabbak et al., 2012).

Beyond birth defects, metals exposure during pregnancy and child development are also known to be associated with neurodevelopmental delays. Lead has been the most widely studied neurotoxic metal with respect to neurodevelopmental disorders, including decreased cognitive abilities and IQ, attention disorders, hyperactivity, and impulsive behavior (Braun et al., 2012; Canfield et al., 2003; Lanphear et al., 2005; Szkup-Jabłońska et al., 2012). Gestational and childhood exposure to arsenic has also been shown to negatively impact neurological development of children (Canfield et al., 2003; Lanphear et al., 2005; Liu, McDermott, Lawson, & Aelion, 2010; Rosado et al., 2007; Wasserman et al., 2004). The magnitudes of these associations are similar to those observed with increases in blood lead, an established risk factor for diminished IQ. Even in areas where residential soil concentrations of arsenic and lead were below standards set by the U.S. EPA, the concentrations of these metals in the soil around mothers' homes during pregnancy affected the severity of intellectual disability in children (McDermott et al., 2014). Little is understood about how combinations of metals interact to influence risk. For example, evidence from McDermott et al. (2014) indicates that the risk of severe intellectual disability differs for differing combination of arsenic and lead.

Adequate nutrient intake during pregnancy, lactation, and early childhood is essential for healthy birth outcomes and child development. For example, iodine plays a crucial role in fetal organogenesis and in particular, brain development. The severity of the outcome depends on the level of prenatal iodine deficiency and ranges from increased neonatal morbidity and mortality, severe mental dysfunction, hyperactivity, and attention disorders to a substantial decrease in IQ (Puig-Domingo & Vila, 2013). Iodine deficiency in early life, ages 5 and younger, has been associated with a reduction in IQ (Bougma, Aboud, Harding, & Marquis, 2013). Birth defects such as neural tube defects including spina bifida (somewhat elevated in Native American populations in the Canfield et al. [2014] study) are strongly associated with folate deficiency (Kancherla, Oakley, & Brent, 2014). Zinc deficiency has been associated with a range of teratogenic, growth retardation, immunologic, and behavioral effects (Uriu-Adams & Keen, 2010). The link between iodine deficiency and development is of particular concern for noncoastal Native communities, as the primary dietary sources of iodine include seafood and dairy products, two components not traditionally a part of those diets. Dietary and biochemical analysis of pregnant and lactating Navajo mothers conducted in 1981 showed marginal deficiencies in zinc, vitamin A, folacin, and iron among these women (Butte, Calloway, & Van Duzen, 1981). The NBCS will be the first study looking at dietary micronutrient sufficiency since then, and current biomonitoring results show more than 40% of mothers are deficient in iodine at enrollment, and more than 78% are deficient in serum zinc.

Is There Potential for Interaction Between Environmental Contaminants and Genetic Factors?

As discussed previously, although genetic factors are frequently linked to birth defects, much existing research fails to look at overall prevalence of these factors in the population, the role of environmental exposures in triggering expression of adverse outcomes, or how these interactions contribute to racial and ethnic differences in birth defects. Data indicating geographic differences in rates of specific defects in the same populations suggest gene–environment interactions might play a significant role in birth defects, but other variables such as cultural, sociodemographic, or reporting and surveillance differences could likewise be contributing to those differences (Weinhold, 2009). Without specific studies on gene–environment interactions, the contributions are difficult to define.

Interactions between genetics and environmental exposures have been hypothesized to play a role in developmental disorders such as autism (London, 2000), with autism spectrum disorder considered a likely candidate for gene–environment interaction. However, the specific nature of the gene–environment interactions in developmental disorders likely arises from complex combinations of genetic and environmental factors (Kelada, Eaton, Wang, Rothman, & Khoury, 2003). Currently, the medical and scientific communities have limited ability to detect the level of risks from gene–environment interactions within specific populations, such as Native Americans, although the understanding of etiologic mechanisms continues to evolve.

Expanding the scientific knowledge base of environmental exposure on human genetics, and subsequent fetal and childhood health, is an important first step toward developing innovative care and resources for Native women and their families. Because many diseases result, at least in part, from complex gene–environment interactions, subtle differences in genetic factors represent different levels of risk to the same environmental exposure (Khoury, Davis, Gwinn, Lindegren, & Yoon, 2005). Therefore, environmental exposures have the potential for far-reaching effects on the developing fetus, beginning at the cellular level of fetal development.

Gene–environment interaction is the interface between genetic and environmental factors (Dempfle et al., 2008), and is often thought of in terms of the same environmental exposures, resulting in differential responses through interactions with different genetic compositions. *Epigenetics* is a term used to describe how genes might interact with their environment to produce observable changes in an individual without changes to the DNA sequence (Waddington, 2012). For example, chemical reactions such as the attachment of methyl groups to DNA can occur as a result of exposure to environmental contaminants, altering how genes are transcribed and in turn expressed, activating or deactivating parts of the genome. These altered

transcription states can be passed on from one generation to the next. Therefore, toxicant exposures might not only have effects on the fetus, infant, and child by epigenetic mechanisms, but epigenetic changes could affect future generations as well (Wallace, 2010), producing heritable effects without changing the genetic makeup.

Given the genetic mutations that have been associated with several developmental disabilities that occur with higher prevalence in the Navajo and other Athapaskan tribes, our lack of understanding of the overall prevalence of these mutations in Native populations, and the high potential for exposures to environmental metals, improving our understanding of gene–environment interactions might be a critical step in understanding the effects of toxicant exposures in Native populations. A genetic susceptibility to a particular developmental outcome that is manifested as a result of environmental exposures, or epigenetic changes resulting from exposures that contribute to that manifestation, would lead to disparities in exposure outcomes that would not be predicted by studies in populations lacking such susceptibility, and not observed in Native populations lacking exposure.

HOW CAN WE FURTHER OUR UNDERSTANDING OF RELATIONSHIPS BETWEEN EXPOSURE AND DISEASE TO ANSWER THE QUESTIONS IN OUR NATIVE COMMUNITIES?

The Navajo Birth Cohort Study

The Pasternak series, originally published as a four-part series in the *Los Angeles Times* in 2006, called attention to the problem of developmental disabilities, such as Navajo neuropathy, and highlighted the communities' concerns about the impacts of the more than 500 abandoned mines (Pasternak, 2006a, 2006b, 2006c, 2006d). As mentioned in the introduction to this article, in 2007, Representative Henry Waxman of California called a hearing on the Navajo abandoned uranium mine situation that led to a 5-year plan to scope and begin addressing the concerns. To better understand the impact of the mine waste on reproductive outcomes and child development, the NBCS was initiated in 2010 to examine any relationships among uranium exposure, reproductive outcomes, and child development. The team anticipates that the results of this ambitious effort will finally provide answers to long-standing concerns, providing not only to Navajo but to other tribal, rural, and international communities a more comprehensive understanding of whether exposures to metal mixtures resulting from abandoned mines can interact with other risk factors to increase disabilities in children in these exposed communities. Enrollment and data collection are in progress. Preliminary findings are discussed here as they pertain to exposure risk factors of primary concern in this article. Developmental assessments and medical

record abstractions are not yet complete enough to determine the relationships between risk factors and outcomes.

The study is funded through a cooperative agreement between the CDC, the Agency for Toxic Substances Disease Registry (ATSDR) and the UNM Community Environmental Health Program (CEHP) with Dr. Lewis as the principal investigator. Additional partners include the nonprofit Southwest Research and Information Center, the Navajo Area Indian Health Service (NAIHS), and the Navajo Nation Division of Health (NNDOH). The project works through integrated teams at all phases, with Southwest Research and Information Center and NNDOH Navajo staff having the primary responsibility for field work, including participant enrollment, outreach, and developmental and environmental home assessments, as well as collection and interpretation of existing environmental data. NAIHS staff participate in recruitment and abstract medical records for all participants as well as collection and processing of blood and urine specimens. CDC/ATSDR provides biomonitoring analysis of blood and urine specimens to confirm exposures, and overall project management. CEHP provides training of all field staff; protocol development and implementation; outreach media development; data management, analysis, and interpretation; and quality assurance. It also conducts mechanistic studies to understand observed relationships between exposures and outcomes.

The study is enrolling pregnant women, interested fathers, and their babies from six NAIHS service units on Navajo Nation. Home environmental assessments, surveys, review of existing data sources, and biomonitoring of blood and urine in mothers, fathers, and babies at multiple times will be used to determine exposures to uranium as well as other metals associated with mine wastes or known to be micronutrients. Medical records of participants will be reviewed, and surveys administered at enrollment and postnatally to identify potential risk factors for reproduction and development. The Ages and Stages Questionnaire Inventory is administered at 2, 6, 9, and 12 months to assess development, with any children with recognized delays referred to GIB for more in-depth evaluation and referral to services. Nutritional data are being assessed by food frequency surveys. Laboratory studies at UNM will follow up key endpoints to investigate mechanisms of toxicity. DNA damage and repair, as well as immune system function and autoimmune disease, will be examined in participants and assessed with respect to patterns and concentrations of metals exposures, as well as other known environmental risk factors, sociodemographic risk factors, and cultural factors to identify contributors to risk and protective factors.

Currently 400 of an anticipated 1,500 families are enrolled in the NBCS. Family units include mothers and children for all, with interested fathers included for approximately half of participating families. Medical record abstraction has begun, but is incomplete and quality assurance is in progress on the initial records. Likewise, the initial developmental assessments are also in the process of quality assurance, with the initial data set under review

to begin the process of norm development by the developers. Although it is too early to draw conclusions from the data for either rates of disabilities, birth outcomes, or effects of exposures, several findings are noteworthy from the ongoing biomonitoring and home environmental assessments.

Metals are measured in blood and urine of mom, dad (when enrolled), and baby at multiple time points. As mentioned, uranium concentrations in the urine of mothers at enrollment show approximately 16.1% of our population exceed the 95th percentile observed for the U.S. population as a whole (NHANES, CDC, 2013). Similar results have been observed in fathers, where 21.6% currently exceed the NHANES 95th percentile. Preliminary results also show that babies are being born with detectable uranium in urine. Limited results with completed analyses to date show 30.1% of the 73 babies tested at birth exceed the adult 50th percentile in NHANES. By 2 to 6 months of age, 75% of 16 children tested to date exceeded the adult 50th percentile, with 18.8% exceeding the 95th percentile. Numbers of analyses are still small, but the trend is disturbing and will be closely monitored as results continue to come in. No data sources are available to use as a reference for these results in children. Although timing of sample collection does not allow for calculation of placental transfer factors, these early data do indicate that babies are being born with uranium, and subsequent measurements through the first year of life also indicate that uranium concentrations in urine can continue to increase throughout the first year of life in some children.

A second unexpected finding has been the observation of iodine deficiency referenced previously. For mothers, 40.2% were iodine deficient at enrollment and 52.7% at delivery, relative to the World Health Organization sufficiency level of 99.0 μg/L (ug/L). As discussed earlier, iodine has been found to be a key nutrient for fetal organogenesis and for brain development. Primary sources of iodine are from seafood and dairy products in the diet. As these are not common dietary components of Native communities in the interior of the country, this raises concerns for sufficiency in other Native populations as well, and suggests a potential intervention that could yield dramatic improvements in developmental outcomes in Native children. Also, the potential for this deficiency to interact with metal exposures, potentially exacerbating effects, is a concern that will be evaluated as birth and developmental data become available.

Despite the observed zinc deficiency in NBCS mothers, at birth, only 12.5% of babies have been deficient, and only 21.6% of fathers. This observation of zinc deficiency in pregnant women is common in many studies internationally and suggests the serum zinc levels are lowered due to transfer to the baby leading to reduction of circulating zinc. The sufficiency of fathers and babies suggests that the deficiency is not a result of inadequate dietary zinc, nor has it been related to reported use of prenatal vitamin supplements. This question is an important area for future study that we will be following up in laboratory studies, as zinc has also been reported to reverse the toxic

effects of arsenic in inhibiting repair of DNA damage (Ding et al., 2009). Preliminary studies in our lab indicate this reversal of toxicity might extend to uranium-induced inhibition of repair of DNA damage as well.

Home environmental assessments have detected uranium in indoor dust samples in 65% of homes tested, and 62% have had at least one metal exceeding screening guidelines based on interagency working group guidelines developed for the World Trade Center (U.S. EPA, 2013a, 2013b), adapted for continuous versus one-time source deposition. Most frequently observed were lead, arsenic, iron, manganese, and antimony. No screening value for uranium is being used, as all observed concentrations are of concern as the focus of this study.

One of the goals of the NBCS is to contribute normative data for the Ages and Stages Questionnaire–Inventory version (ASQ–I) to better understand development of Native American children. The ASQ–I is a developmental screening tool currently used by a variety of professionals to track a child's development in various domains at a specific age or over a period of time. In collaboration with the developers of the ASQ–I, data collected from this instrument will be used to establish a set of normative data for this developmental measure specific to our Navajo population. To our knowledge, this will be the first time that longitudinal data have been collected from a cohort of Navajo children to track development within the first year of life. Because the ASQ is so widely used in both clinical and research settings, including by GIB, these data will be valuable for understanding potential developmental differences in this population and guiding referral and intervention practices in a manner that better reflects cultural differences.

CONCLUSIONS

Existing data demonstrate (a) a strong potential for exposures to metal mixtures associated with mining wastes in Native American populations in the Western United States, (b) a linkage of exposures to developmental disabilities and congenital malformation in population and laboratory studies, (c) higher rates of several congenital anomalies in Native American populations, and (d) a lack of comprehensive data on rates and types of developmental disabilities in Native populations.

Although data discussed here indicate a strong reason for concerns about the impacts of environmental exposures in Native American and Alaska Native communities, the NBCS will be the first comprehensive examination of these questions. The results should have a significant impact on our understanding of the complexities and unique aspects of not only environmental exposures, but their interaction with other socioeconomic, demographic, and cultural variables in determining reproductive and developmental outcomes. Although tribes make up a small proportion of the U.S.

FIGURE 4 Helen Nez and her daughter Seraphina.

population as a whole, they are neglected in the body of literature we use to inform our policies and decisions. Their connection to the land, the extent of environmental contamination, and the occurrence of many socioeconomic factors associated with health disparities, as well as their unique genetics, make it critical to understand the causes of developmental delays, adverse birth outcomes, and ultimately disabilities in these populations where determinants might interact in unique ways, and where services remain limited.

In the words of Helen Nez (shown in Figure 4):

> We are veterans of war. We gave a lot to help Washington, DC. Our children had to become warriors. This land that we live on and whatever they mined from it is a Navajo legacy. Because we helped in this way, people became sick and many now suffer from long-term exposure. We did not know that the uranium was going to hurt other people, too. Because we did not know about the dangers we were played with like toys. We were moved around in a game of war. There is beauty. How we value our mother the land. She is filled with sacred elements. Her elements that protect our people protected the United States: this history has not been told right. We have been wounded with the land. Our children, and our grandchildren: we do not know what will happen in the future to our children.

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